USE OF FRESH FROZEN PLASMA AT HOSPITAL SELAYANG: A RETROSPECTIVE STUDY

BY

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DECLARATION

I hereby declare that this research has been sent to Universiti Sains Malaysia for degree of Masters of Transfusion Science. It is also not to be sent to any other universities. With that, this research might be used for consultation and will be photocopied as reference.

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LIST OF SYMBOLS

%	Percent
=	Equal to
≥	More than and equal to
≤	Less than and equal to
>	More than
<	Less than
°	Degree
µ	Micro
±	Plus minus
≈	Almost equal to

LIST OF ABBREVIATION

A & E	Accident & Emergency
APTT	Activated Partial Thrombin Time
BTS	Blood transfusion service
FFP	Fresh Frozen Plasma
HPB	Hepato Pancreator Biliary
INR	International Normalized Ratio
NBC	National Blood Centre
O & G	Obstetrics and gynaecology
PT	Prothrombin Time
TACO	Transfusion associated circulatory overload
TAGVHD	Transfusion associated graft versus host disease
TAS	Transfusion associated sepsis
TRALI	Transfusion related acute lung injury
ug/dl	Micro gram per decilitre
WHO	World Health Organization

ABSTRAK

KAJIAN RETROSPEKTIF: PENGGUNAAN PLASMA BEKU SEGAR DI HOSPITAL SELAYANG

Latarbelakang. Transfusi plasma beku segar telah meningkat dan menjadi popular kebelakangan ini. Ia telah mula digunakan sejak tahun 1920-an dan apabila digunakan dengan indikasi yang betul ia dapat menjadi satu rawatan moden yang membantu dalam penyembuhan pesakit. Namun transfusi plasma darah juga boleh mendatangkan kemudaratan kepada pesakit seperti alergik, *TRALI, TACO* dan jangkitan penyakit berjangkit. Oleh itu, kajian ini dijalankan untuk mengenal pasti indikasi yang betul mengikut garis panduan yang telah ditetapkan bagi transfusi plasma beku segar.

Objektif. Menilai indikasi transfusi plasma beku segar samada mengikut garis panduan ataupun tidak kepada pesakit yang menerima transfusi darah di Hospital Selayang. Garis panduan yang digunakan adalah dari Pusat Darah Negara dan *College of American Pathologist*.

Kaedah. Kajian retrospektif di kalangan pesakit dewasa yang terlibat di dalam transfusi plasma beku segar di Hospital Selayang antara Januari 2016 sehingga Disember 2016. Data diambil dari sistem komputer yang dikenali sebagai *total hospital information system (THIS)* borang permintaan darah dan borang reaksi transfusi darah.

Keputusan. Sejumlah 373 pesakit telah disertakan di dalam kajian ini, dan sebanyak 73.2% keputusan adalah mengikut indikasi manakala 26.8% keputusan tidak mengikut indikasi. Jabatan Hepato Pancreator Biliari dan Ortopedik merupakan jabatan yang paling banyak melakukan transfusi plasma beku segar tanpa mengikut

indikasi. Bacaan *INR* yang normal pula menunjukkan 3.22 kebarangkalian untuk diberikan kepada kumpulan yang tidak mengikut indikasi. Transfusi reaksi yang terbanyak adalah alergik dan demam yang tidak disebabkan oleh reaksi hemolisis (*febrile non haemolytic reaction*).

Kesimpulan. Transfusi plasma beku segar tanpa mengikut indikasi mendedahkan pesakit kepada risiko reaksi transfusi dan ia patut dicegah dan dikawal sehabis baik. Hasil penemuan di dalam kajian ini diharapkan dapat memberi manfaat kepada para doktor di dalam membuat keputusan yang betul ketika transfusi darah diperlukan.

ABSTRACT

USE OF FRESH FROZEN PLASMA AT HOSPITAL SELAYANG: A RETROSPECTIVE STUDY

Background. FFP transfusion has increased in demand over the years and the global trending of high FFP usage can be seen in many countries. It has been used since 1920's and if appropriately used, it can improve the quality of life. However FFP transfusion is not without risk. It may cause adverse transfusion reaction such as allergic reaction, TRALI, TACO and transfusion transmitted infections. Thus this study was conducted to assess the indication of FFP transfusion against the guideline available.

Objective. To assess the appropriateness of the use of fresh frozen plasma at Hospital Selayang against the National Guideline for the rationale use of blood and blood products and international guideline by College of American Pathologist.

Method. A retrospective study among adult patients receiving fresh frozen plasma from 1 January 2016 until 31 December 2016 by reviewing total hospital information system (THIS), blood order and transfusion reaction forms. The appropriateness of requests was assessed against existing guidelines. The percentage of indicated diagnosis (appropriate) and not indicated diagnosis (inappropriate) FFP transfusions were obtained.

Result. Total of 373 patients receiving FFP were included in this study. About 73.2% of the patients were given FFP with indicated diagnosis and is considered appropriate while 26.8% was inappropriate. HPB and Orthopaedic are the most departments to transfused FFP inappropriately. Those with normal INR were 3.22 times higher odds of being inappropriate for FFP transfusion compared to those with

prolong INR readings. Total of 4.3% patients developed transfusion reaction mainly mild allergic and febrile non hemolytic reaction (FNHR).

Conclusion. Inappropriate transfusion exposes patient to unnecessary adverse event and thus should be monitored and prevented by all means. The findings of this study are beneficial to justify the role of clinicians in making the right decision in transfusion practices.

CHAPTER 1

INTRODUCTION

1.1 Title

Use of Fresh Frozen Plasma at Hospital Selayang: A Retrospective Study

1.2 Overview

Transfusing blood and blood component has become an essential part of modern health care. In appropriate usage, it can improve the quality of life and prevent morbidity and mortality (National Blood Centre, 2010). However, blood transfusion comes with major problems concerning over safety, cost and availability. Despite meticulous process and procedures in place to ensure blood safety, the risk of complication still remains. Therefore, it is very important to comply the guidelines. All health care professionals who are involved in patient management need to comply with transfusion practices, guidelines for appropriate blood use, the availability of particular blood products and patient specific blood product needs (Shander and Goodnough, 2007).

Blood Transfusion Services (BTS) aim to provide 'safe and adequate' blood at any time (National Blood Centre, 2016). To achieve this goal, BTS is governed by national blood policy and legislative framework to promote uniform implementation of standards and consistency in the quality and safety of blood and blood products. According to WHO in 2013, 122 out of 179 (68%) of reporting countries all over the world had a national blood policy. In Malaysia, 'Transfusion Practice Guidelines for Clinical and Laboratory Personnel' and 'Guidelines for the Rational Use of Blood and Blood Products' have been established following relevant requirements of

established standards such as MS ISO 15189, current Good Manufacturing Practice (GMP) and Good Clinical Practice (GCP). These guidelines served as a comprehensive guidance for blood transfusion practices and guidelines for appropriate blood used. Despite of having a clearly defined guideline, patients continue to received unnecessary transfusion every day (Asif et al., 2013).

Furthermore, the availability of blood and blood product is also an important aspect to be considered. Blood is a limited resource and it is important to rationalize and optimize transfusion practice (Roback et al., 2008). According to Dr S. Subramaniam (Ministry of Health) in Malay Mail, only 2.2% of Malaysian population is a blood donor (Edward, 2015). According to United Nations, the current population of Malaysia is 30,906,650 as of November 2016. About 2.2% of this current population makes only about 600,000 Malaysians are blood donor. The percentage of Malaysian blood donor is low compared to the recommendation by WHO which is 3.5%-5% of the population in developing countries.

Blood is obtained from voluntary, non-remunerated blood donors. An anticoagulant is used enabling them to be stored and transfused to a patient. Two collection methods are used; whole blood donation and apheresis donation. Whole blood donation is separated into multiple component such as red cell, platelet and plasma while apheresis is the collection of a specific blood component by a specialized cell separator machine that centrifuges the donor's whole blood, separates and removes the desired component (plasma, platelets, RBCs, or granulocytes) and returns all other blood components to the donor (Norfolk, 2013). Nowadays, blood can be used more effective if it is processed into components such as red cell concentrate, platelet concentrate, plasma, cryoprecipitate and

cryosupernatant. By performing blood component processing, the need of more than one patient can be meet (WHO, 2017). Since components transfusion is said to be more effective, fresh frozen plasma as one of the blood components was chosen to be studied.

Frank Hartman performed the first plasma transfusion to treat the Spanish flu in 1918. In the late of 1920's and 1930's plasma started to become routinely used in hospitals. Within the era, plasma was produced in two forms which were dried and frozen and studies showed both were just effective and much easier to store. However during World War II, United State army used dried plasma as a blood substitute but it was found that manufacturing of dried plasma causes prothrombin depletion. Thus, fresh frozen plasma has become a more superior product (Puetz, 2013).

Fresh Frozen plasma (FFP) is a plasma product derived from human collected via whole blood or apheresis donation. It is prepared by freezing it at -18°C or colder within 8 hours of collection and can be stored for a year (Bucur and Hillyer, 2001). FP24 is plasma unit that is frozen within 24 hours after collection and is commonly practiced in the United State (Eder and Sebok, 2007). FFP is thawed at 30°C to 37°C and once thawed the shelf life is 5 days when stored at 1°C to 6°C (Triulzi and Yazer, 2010). The practice of FFP production in Malaysia as stated in Transfusion Practice Guideline is described in table 1.

Table 1: Definition, criteria, preparation method, storage and shelf life of FFP

Component	FFP
Definition	A component which contains labile clotting factors and other constituents, for transfusion or fractionation.
Criteria for preparation	Duration of whole blood donation shall not exceed 15 minutes. Plasma should be prepared within 24 hours of whole blood collection, preferably within 12 hours.
Preparation	Plasma is obtained from whole blood after centrifugation, or by plasma apheresis and immediately frozen to achieve complete freezing within 1 hour to a core temperature of below minus 30°C (-30°C).
Storage temperature and shelf life	a. 36 months at or below -25°C (≤-25°C). b. 3 months at -18°C to -25°C.

The content of FFP include immunoglobulin, albumin, coagulation factors and fibrinolytic proteins, ionic solutes and trace elements (Basu and Kulkarni, 2014). FFP prepared from whole blood and apheresis donation may differ only in the quantity of plasma in the pack. The volume may vary from 180ml to 400ml (O'shaughnessy et al., 2004).

According to John Puetz, the typical amount of FFP used in adults is 2 units, with a unit of FFP derived from whole blood donation of a single donor. A unit of FFP is about average of 200ml (Puetz, 2013). FFP dose can also be calculated using dose of 10-15ml of plasma per kg body weight. However the dose can exceeded in the case of massive bleeding. Hence , FFP dose relies on patient clinical condition,

plasma volume and the target increment of coagulation factors in post transfusion patient (O'shaughnessy et al., 2004).

FFP transfusion is not without risk, and certain complications are more likely to occur in FFP transfusion compared to other blood components for example transfusion related lung injury (TRALI), transfusion associated circulatory overload (TACO), allergic or anaphylactic reactions. Other less common complications are transmitted transfusion infection (TTI) such as HIV, HepB, HepC or syphilis, febrile non haemolytic transfusion reaction, Red blood cell (RBC) allo-immunization and haemolytic transfusion reaction (Pandey and Vyas, 2012). FFP has also been linked with transfusion associated graft versus host disease (TAGVHD) and transfusion related mortality (Vamvakas and Blajchman, 2009).

Although transfusion of FFP is associated with multiple adverse effects and risks ranging from mild to possible fatal outcome, the global trending of FFP usage has increased through years and all around the world. In United States (US), 2.3 million units of FFP were transfused in 1991 and increased to 3.9 million in 2001. In 2008, 4.5 million unit of FFP were transfused which was 11.8% increased from 2006 (Pandey and Vyas, 2012). In United Kingdom (UK), high trend of FFP usage has been observed too. British Safety Hazards of Transfusion (SHOT) annual report from 2010 to 2015 stated that total of 266,332 units of FFP were transfused in 2013, followed by 247,466 in 2014 and 232,902 in 2015 (refer to Table 2). High trend of component usage can also be seen in Australia. According to Australian Haemovigilance Report (Data for 2011-2 and 2012-13), the decreasing trend in demand of FFP usage was probably because of improving success of appropriate usage and reducing wastage (National Blood Authority Advisory Committee, 2015).

Table 2: Units of FFP transfused since 2010 until 2015 reported in Safety of Hazards Transfusion (SHOT) annual report in UK

Year	Red Blood Cells	Platelets	FFP	Cryoprecipitate	Totals
2010	2,180,781	246,962	**292,884**	120,311	2,840,938
2011	2,162,137	301,628	**288,242**	126,170	2,878,177
2012	2,146,783	311,737	**282,721**	44,108	2,785,349
2013	2,043,046	312,140	**266,332**	43,957	2,665,475
2014	1,966,866	318,539	**247,466**	43,156	2,576,027
2015	1,893,812	310,673	**232,902**	43,645	2,481,032

Table 3: Units of FFP transfused since 2009 until 2013 in Australian Haemovigilance Report (National Blood Authority Australia)

Year	Red Blood Cells	Platelets	FFP	Cryoprecipitate	Totals
2009 to 2010	795,892	128, 495	**160,813**	64,734	225,547
2010 to 2011	800,570	134,705	**160,537**	70,102	230,639
2011 to 2012	801,295	134,149	**159,024**	78,099	237,123
2012 to 2013	763,542	134,576	**147,641**	85,692	233,333

Hospital Selayang received the resources of blood and blood component from National Blood Centre (NBC). Table 4 shows the unpublished data of FFP usage in Hospital Selayang since 2012 until 2016. Increased demand for FFP could be seen in three consecutive years from 6,075 in 2013 to 6,424 in 2014 and 6,881 in 2015. This increasing in demand raised a question on appropriateness of FFP transfusion and whether the judgement made based on patient benefit or assumption only. It also raises our concern on the risks of transfusion reaction including the under reported adverse events.

Table 4: Unpublished data Units of FFP transfused in Hospital Selayang since 2012 until 2016

Year	FFP
2012	**6,416**
2013	**6,075**
2014	**6,424**
2015	**6,881**
2016	**6,497**

The numbers of cases for FFP related transfusion reaction were 36 cases in 2015 and 30 cases in 2016. . The most common type of reaction was allergic and febrile non haemolytic reaction. Table 5 and 6 summarized transfusion reaction (unpublished data) in Hospital Selayang for 2015 and 2016.

Table 5: Unpublished data type of product involved in transfusion reaction in hospital selayang for 2015 and 2016

Year	Type of products involved in transfusion reaction (n)				
	Whole blood	RBC	platelet	**FFP**	Cryoprecipitate
2015	2	135	6	**36**	0
2016	0	113	4	**30**	0

Table 6: Unpublished data type of transfusion reaction occur in Hospital Selayang in 2015 and 2016

Type of transfusion reaction	**2015**	**2016**
Allergic	**85**	**69**
Anaphylactic	1	0
Febrile non haemolytic	**84**	**70**
Acute/delayed haemolytic	0	0
TACO	1	1
TRALI	0	0
Bacterial contamination	0	0
Others	8	7

1.3 Literature Review

1.3.1 Introduction

FFP is a blood product produce from plasma that is separated from packed red cells and platelets after centrifugation of whole blood donation or apheresis donation frozen at -30°C within 6 to 8 hours of phlebotomy (Razzak et al., 2014). It had been introduced into clinical practice and was initially used as volume replacement therapy during World War II by US army. Better understanding of the clinical use of FFP has contributed to the change in practice of FFP transfusion through time. Generally, FFP is frequently used to either as prophylaxis before invasive procedure or surgery to prevent bleeding or as therapeutic to stop bleeding (Stanworth et al., 2007)

Human plasma has more than 120 proteins that are involved in transportation, enzymatic activities and haemostasis. One ml of plasma contain approximately 5-10µg von willebrand factor (VWF), 2-3mg fibrinogen and coagulation factors II, VII, IX, X, VIII (Bucur and Hillyer, 2001). FFP is rich with coagulation labile factor mainly factor V and factor VIII (Chng et al., 2003). FFP consist all coagulation factors rationalized the fact that it is useful to arrest bleeding due to coagulapathy.

FFP should be given closed to the time of invasive procedure or surgery if correction of coagulopathy is required since the half life of some coagulation factor are short. FFP stored at -80°C can last for 36 months however once thawed, FFP shelf life reduced to 5 days when it is kept at 1-6°C and it is recommended to be used within 24 hours (Donegan et al., 2008).

1.4 Clinical indication of FFP

The global trending of FFP transfusion has increased over the years despite the lack of scientific rationale and the potential harm (Liumbruno et al., 2009). Historically, during the World War II, besides treating trauma, varieties of indication including sepsis (to neutralize toxin, not to treat coagulopathy), burn, nutritional deficiencies, nephrotic syndrome, sickle cell anaemia and acute lymphoblastic anaemia (ALL) (Puetz, 2013). Later , the administration of FFP is considered appropriate in patient with (Shander and Goodnough, 2007):-

1. Prolonged PT or INR is greater than 1.5 in patient scheduled for invasive procedure and surgery
2. During massive haemorrhage when INR exceeds 1.5
3. Patient with thrombotic thrombocytopenic purpura (TTP)
4. for treatment of inherited coagulopathies
5. for which there are no specific concentrates available
6. for anticoagulant-related bleeding

It is then been confined to two main indications which are prophylactic to prevent bleeding in patient with coagulopathy before invasive procedure or surgery or as therapeutic to treat bleeding patients (Stanworth et al., 2007). Recommendation of FFP transfusion has been consistent in most guideline despite of having some variability in local guidelines. According to Guidelines for the rational use of blood and blood products (National Blood Centre, 2010), the recommended FFP transfusion includes:

1. For replacement of single factor deficiencies where specific or combined factor concentrate is not available.

2. For immediate reversal of warfarin effect in the presence of potentially life-threatening bleeding when used in addition to vitamin K.

3. For treatment of multiple coagulation deficiencies associated with acute disseminated intravascular coagulation.

4. For the treatment of thrombotic thrombocytopaenic purpura.

5. For the treatment of inherited deficiencies of coagulation inhibitors in patients undergoing high risk procedures where specific factor concentrate is unavailable.

6. In the presence of bleeding and abnormal coagulation parameters following massive transfusion or cardiac bypass surgery or in patients with liver disease.

The commonest inappropriate indication is to treat patients with abnormal coagulation tests who are not bleeding. An elevated PT/INR and APTT is presumed to be caused by coagulation factor deficiency and will cause increased risk of bleeding. FFP then should replace the coagulation factor deficiency and reduce risk of bleeding. While completely logical, this reason is based on assumptions which are incorrect (Holland and Brooks, 2006).

1.5 Administration of FFP

FFP adequate dosage in most literature or guidelines is 10-15ml/kg or equivalent to 3-4 unit of FFP (Chaudhary et al., 2005). The typical volume of FFP derived from whole blood donation is about 200ml. American of Association of Blood Bank (AABB) guidance in the setting of massive transfusion is to use FFP if INR is greater than 1.5 (Roback et al., 2008). Factor level begins to drop below 30% as INR level prolong to more than 1.6. The administration of thawed FFP must be within 24 hours since some coagulation factor deteriorates over time such as factor VII that has half life of 4-6 hours (Yazer, 2010).

1.6 The significant of abnormal coagulation parameters to guide FFP transfusion

The principles of coagulation parameters must be understood to determine or guide for FFP transfusion. PT and APTT was first developed to investigate coagulation factor deficiencies, not to predict bleeding (Stanworth, 2007). PT and APTT are widely used global screening tests for blood coagulation. The end point for both tests are assessment of thrombin generation. They do not represent the comprehensive assessment of haemostasis. PT represent extrinsic pathway while APTT represent intrinsic pathways of the in vitro coagulation cascade (Bajaj and Joist, 1999). In vivo, however is more complex. The whole process of haemostasis is complicated by both pathways, platelet activation and vascular elements (Chee et al., 2008).

Both tests are usually affected by pre-analytical and analytical variables particularly the reagent use, technique and quality control of the laboratory. The

technique involved recording of clot formation time, mechanical, electromechanical or optical system. The normal reference range of APTT is 20-45 seconds while PT is 10-14 seconds however this value varies for every hospital since it is generated from the establishment that is based on population value. Result for both tests may be outside of normal range because of certain factors such as biological variation of different individuals.

Some conditions associated with both prolonged PT and APTT are severe liver disease, severe vitamin K deficiency, low-moderate intensity warfarin therapy (INR>2.5) and severe DIVC (Bajaj and Joist, 1999). PT is prolonged in more advanced liver disease because hepatic parenchymal cells are responsible to synthesized all clotting factors involved in extrinsic and common pathway. In DIVC, consumption of factor VIII, V and fibrinogen that interfere with fibrin polymerization lead to prolongation of PT (Bajaj and Joist, 1999).

PT is commonly used to monitor certain anticoagulant therapy because it is sensitive to warfarin-induced decreases in the vitamin K dependent factor VII, X and prothrombin. The presences of human type tissue thromboplastin in PT reagent vary in sensitivities and thus may contribute to prolongation of PT too. Some reagent result in prolongation of coagulation time only when a relevant factor level drop to less than 30iu/dl. A controversial statement that PT is useful only for patient on Vitamin K antagonist and not useful for other condition such as liver disease is debateable (Tonna et al., 2007). PT result has been greatly improved with the introduction of International normalized ratio (INR). The acceptable and common practice by many clinicians is INR≥1.5 to initiate FFP transfusion.

One study showed the relation between INR range and mean coagulation factor levels. For example, when INR is 1.3-1.9, mean coagulation factor levels for Factor II are 31-65%, Factor V is 70% and factor VII is 22-60%. They are considered sufficient to support haemostasis (Deitcher, 2002).

Segal and Dzik (2005) performed and evidence based review of the ability of INR to predict bleeding from an invasive procedure taken from 25 studies (one from clinical trial and 24 from observational studies)(Segal and Dzik, 2005). It was found that bleeding rate of patients with or without abnormal coagulation was similar for some invasive procedure done and risk difference calculated showed little absolute difference. Hence, the author concluded that abnormal coagulation test does not predict bleeding in all patients.

1.7 Adverse reactions of FFP transfusion

In Hospital Selayang, a total of 6,881 and 6,497 units of FFP were transfused for 2015 and 2016 respectively. Transfusion reaction cases reported in 2015 was 179 while in 2016 was 147 cases. Out of 179 cases in 2015, 20% of the reaction is caused by FFP. The percentage is similar for 2016 (30/147 cases). The most common reactions are allergic and febrile non haemolytic reaction (unpublished data of Hospital Selayang).

Besides, FFP transfusion also caused transfusion transmitted infection such as HIV, Hepatitis B, Hepatitis C and Syphilis. In Hospital Selayang, unpublished data from 2012 to 2016 shows 6 suspected seroconverted cases causes by FFP transfusion were investigated. Out of these 6 cases, 3 cases cannot be determine since patients

had passed away, 2 cases is still in ongoing investigation and 1 case is negative for the suspected infection which is HIV.

Adverse transfusion reaction also includes actual error such as wrong blood administered to wrong patient. This reaction may result from acute haemolytic reaction to organ failure and worst, fatal complication that may caused death. In order to provide an intensive and effective haemovigilance programme, near misses must also be reported. According to Malaysian Patient Safety Goals: Guidelines on Implementation & Surveilance by Kementerian Kesihatan Malaysia in 2013, near misses means any error which if undetected could result in the determination of a wrong blood group or transfusion of an incorrect component but was recognized before transfusion took place (Patient Safety Council, 2013).

Transfusion error and near misses has reduced in numbers over the past few years in Hospital Selayang (Table 7). The main problem that causes transfusion error and near misses is failure to identify patient in every significant step took place such as prior to blood taking activities and transfusion itself. Tremendous effort has been made by Blood Transfusion Unit and Hospital Transfusion Committee (HTC) to overcome the problem such as conducting Transfusion Safety Workshop every year, implementing transfusion checklist, continuous medical education (CME) for all housemen and counselling as well as extension of houseman period

Table 7: Summary of Transfusion Error and Near Misses from 2009 – 2016 in Hospital Selayang (unpublished data)

Types of Error	**2009**	**2010**	**2011**	**2012**	**2013**	**2014**	**2015**	**2016**
NEAR MISSED								
Labelling & Sampling Error	19	10	5	5	4	4	4	3
Error in Blood Bank	4	1	0	1	0	0	1	0
INCIDENTS								
Discrepancy in Patient Info	0	0	0	1	2	4	3	2
Previous Error	10	7	2	0	0	4	1	5
TRANSFUSION ERROR								
Wrong blood given to wrong patient	1	0	0	0	0	1	1	2
Uncross matched blood given to patient	0	1	0	0	0	0	0	0
TOTAL	**34**	**19**	**7**	**7**	**6**	**13**	**10**	**12**

Other risks commonly associated with FFP transfusion include transfusion related lung injury (TRALI), transfusion associated circulatory overload (TACO), transfusion associated sepsis (TAS), TAGVHD, haemolytic transfusion reaction (HTR) and increased in mortality and morbidity.

1.7.1 Transfusion related acute lung injury (TRALI)

TRALI has emerged as the leading causes of transfusion related mortality reported by FDA in 2013. According to United Kingdom's Serious Hazards of Transfusion (SHOT) hemovigilance data from 2003, TRALI risk was 6.9 times higher in FFP than in red cells. TRALI presented with acute hypoxemia and non-cardiogenic pulmonary oedema during 6 hours of transfusion. Most patients recover within 3 days with respiratory support, however 5-25% cases are fatal. According to Rossi's Principles of Transfusion Medicine, patient will experience respiratory distress such as shortness of breath, tightness in chest and dry cough. Patient often become hypoxic, hypotensive and tachycardia (Simon et al., 2016).

Antibodies towards HLA antigen is the culprit in causing TRALI. Majority of cases (75-90%) were associated with HLA antibodies with 50% directed against HLA class II antigen (Win et al., 2008). About 10 to 25% of TRALI caused by antibodies to human neutrophil antigen (HNA). When leukocytes antibodies are transfused into a patient with cognate antigen, HLA class II and HNA antibodies (mainly HNA 3a) will indirectly activate neutrophil via monocyte activation and cytokine release. Neutrophils within the pulmonary microvasculature will then agglutinate and release enzymes, reactive oxygen species, and inflammatory mediators which injured the pulmonary endothelium (Pandey and Vyas, 2012).

The main strategy used to mitigate TRALI is to implement male-only plasma strategy since most donors implicated to TRALI were multiparous women and approximately 17% of female donor has leukocyte antibodies (Pandey and Vyas, 2012). Risk of antibodies increases with more pregnancies. Many countries have implement this strategy such as UK, US, German, Canada and Netherlands. It is proven by many studies that by implementing this strategy, TRALI has reduced in number. One of the studies done is from American Red Cross that showed TRALI incidence become 1:250,000–317,000 (post mitigation) from 1:51,000–65,000 plasma units issued pre-mitigation. In Netherland, a reduction of 33% of TRALI incidence after male only plasma strategy was implemented (Wiersum-Osselton et al., 2011).

1.7.2 Transfusion associated circulatory overload (TACO)

TACO is similar to TRALI where it characterized as acute respiratory distress, hypoxia, pulmonary oedema temporarily associated with transfusion. However TACO is a hydrostatic not permeability oedema. There is no distinct clinical finding or test that can differentiate between TACO and TRALI but there are some signs and symptoms that can help such as chest x-ray, echocardiography and pulmonary artery occlusion pressure (Pandey and Vyas, 2012). TACO has received little attention in literature until recently in 2010, TACO was the second leading cause for mortality in the US as being reported in FDA/CBER: Fatalities reported to the FDA following blood collection and transfusion: Annual summary for fiscal year 2010 (Food and Administration, 2011). TACO has been reported to be caused by a single red cells transfusion however, plasma transfusion is also a risk factor for TACO since large volume is usually needed in adult. TACO usually occurred in

cases of massive transfusion where large amount of blood and blood products are transfused to patient (Payandeh et al., 2013).

1.7.3 Allergic/ anaphylactic transfusion reaction

Allergic reaction is a common transfusion reaction due to various protein antigens present in plasma that can be a problem but rarely life threatening. Anaphylactic is characterized by systemic symptoms of bronchospasm, angioedema, and/or hypotension and estimated incidence ranges from 1:18,000 to 1:172,000 transfusions (Pandey and Vyas, 2012). According to SHOT 2015 annual report, total number of reaction reported was 296, where 122 was because of allergic reaction (second highest after febrile-typed reaction = 142).

1.7.4 Transfusion associated graft versus host disease (TAGVHD)

TAGVHD is not typically associated with plasma transfusion since FFP is considered non-cellular. It is usually fatal and is caused by viable lymphocytes within a transfused product which engraft and proliferate within the transfusion recipient. Fortunately, TA-GVHD is rare and has never been reported with FFP (Pandey and Vyas, 2012). It has been estimated that TA-GVHD can occur with as few as 80,000 transfused lymphocytes, but a thawed plasma unit is unlikely to contain that number of viable lymphocytes (Sachs, 2010).

1.7.5 Transfusion associated sepsis (TAS)

Blood is a good medium for bacteria growth and once contaminated it can cause death to the recipient. Plasma typically are not contaminated with bacteria since it is in frozen state. However the thawing process can easily exposed plasma to bacterial contamination. One study in German reported that five cases of bacterial contamination in plasma were found from 1997 to 2007 (Keller-Stanislawski et al., 2009). According to Keller-Stanislawski et al, organism identified included species of *Staphylococcus, Klebsiella, Propionibacterium, and Psuedomonas*. Waterbaths used to thaw plasma are a potential source of contamination, and pseudomonas has been cultured from frozen products thawed in contaminated waterbaths (Pandey and Vyas, 2012). Care must be taken to properly clean and sterilize waterbaths regularly, and plasma should be transfused as soon as possible after thawing.

1.7.6 Haemolytic transfusion reaction (HTR)

Transfusion of an ABO incompatible plasma unit may cause a HTR, especially if the donor has high titer isohemmagglutinins. There have been multiple case reports of HTR after transfusion of a single unit (~200ml) of ABO-plasma incompatible platelets (i.e. Type O platelet to a Type A patient) (Pandey and Vyas, 2012). To prevent HTR, transfusion service provides ABO compatible FFP to patients. If it is not available, FFP of a different ABO group that does not contain high titer anti-A or anti-B may be used (O'shaughnessy et al., 2004).